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ORIGINAL RESEARCH INTENSIVE CARE

C-reactive protein/albumin ratio versus lactate/albumin ratio as an outcome predictor for patients with sepsis and septic shock in hospital stay

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ABSTRACT

Background & Objective: Pre-emptively identifying individuals at risk of developing sepsis and septic shock remains challenging. In septic patients, the Lactate/Albumin Ratio (LAR) and C-reactive protein (CRP)/Albumin ratio (CAR) have been suggested to be promising prognostic indicators for prediction of intensive care unit (ICU) mortality. We compared the prognostic values of CAR and LAR in patients with sepsis and septic shock.

Methodology: Eighty adult patients diagnosed with sepsis and admitted to the ICUs of Ain Shams University Hospitals, were included in this observational prospective study. CRP levels, serum lactate, serum albumin, complete blood count (CBC), procalcitonin levels, and SOFA scores were assessed upon admission, with subsequently observing 28-day mortality among the selected patients.

Results: CAR values were comparable between the mortality and survival groups (P = 0.807). However, LAR values were significantly elevated in the mortality group vs the survival group (P = 0.044). ROC analysis for mortality indicated that LAR had an AUC of 0.633 at a cutoff value > 0.68, achieving sensitivity and specificity of 89.4% and 21.2%, respectively. In contrast, CAR had an AUC of 0.484 at a cutoff value ≥ 1.54, with sensitivity and specificity values of 63.8% and 57.6%, respectively. Length of ICU stay (P < 0.001), duration of mechanical ventilation (P < 0.001), cardiovascular support (P < 0.001) and the need for renal replacement therapy (P < 0. 039), were increased in the mortality group compared to the survival group.

Conclusion: Lactate/albumin ratio is superior and more reliable bio-marker predictor compared to C-reactive protein (CRP)/albumin ratio for ICU mortality.

Abbreviations: CAR - C-reactive protein/albumin ratio; CRP - C-reactive protein; ICU - intensive care unit; LAR - Lactate/Albumin Ratio;

Keywords: Albumin; CRP To Albumin Ratio; Lactate; Lactate to Albumin Ratio; Mortality; Sepsis; Septic Shock; SOFA; Survival

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1. INTRODUCTION

Sepsis is a syndrome resulting from an uncontrolled inflammatory response to infection. The associated biological, physiological and biochemical abnormalities lead to multi-organ dysfunction and increased mortality rates.[1,2] Sepsis is characterized by severe inflammation resulting in microcirculatory disorders, including platelet activation and endothelial cell damage. Tissue hypoxia eventually results in lactic acidosis, a common finding in patients with sepsis.[3]

Accordingly, predictive biomarkers of mortality are needed for early detection and treatment, aiming for better clinical outcomes. High lactate levels are linked to unfavorable outcomes and increased mortality, making them useful for risk stratification and early diagnosis in patients with sepsis.[4]

Albumin (Alb) is a crucial protein in the body. In addition to maintaining acid base balance, albumin transports various exogenous and endogenous substances, such as hormones and drugs.[5] While both lactate and albumin levels independently predict mortality, recent studies have shown that the Lactate/Albumin Ratio (LAR) is a superior predictor compared to albumin or lactate alone.[6-8]

C-reactive protein (CRP) is primarily used as a marker of inflammation. Few factors, aside from liver failure, are known to interfere with CRP production.[9] According to previous studies, C-reactive protein/albumin ratio (CAR) is considered a superior predictor compared to CRP or albumin alone.[10,11]

We compared C-reactive protein/albumin ratio with lactate/albumin ratio as an outcome predictor for patients with confirmed sepsis and septic shock and admitted in hospital ICU.

2. METHODOLOGY

After obtaining approval of the local ethical committee (FMASU No. MD287a/2022/2023) and registration of the clinical trial at PACTR202312493987501, this observational prospective study was carried out in the surgical and medical intensive care units from November 2022 to December 2023 on patients aged 21-80 y diagnosed with sepsis and requiring ICU admission at Ain Shams University Hospitals. The diagnosis was made in line with The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[1]

Exclusion criteria included patient refusal, pregnancy, malignancy, intestinal resection surgeries, and other pathologies that may alter serum albumin levels prior to ICU admission (e.g., cirrhosis, nephrotic syndrome and malnutrition).

All participants included in the study were thoroughly examined, level of consciousness assessed, hemodynamics and arterial oxygen saturation measured, sequential organ failure assessment (SOFA score) calculated based on six different independent scores (respiration, cardiovascular, renal, hepatic, coagulation profile, neurology), medication usage (including vasoactive medications), and laboratory tests reviewed.

2.1. Sample size

Using PASS 11 program for sample size calculation, reviewing results from the previous studies, showed that mortality rate among patients diagnosed with sepsis was 50%.[12-13] Assuming area under curve (AUC) = 0.7 for lactate/albumin ratio for prediction of mortality among septic patients, and after 20% adjustment for dropout rate a sample size of at least 80 participants achieved 80% power to detect a difference of 0.2 between the area under the AUC under the null hypothesis of 0.5 and an AUC under the alternative hypothesis of 0.7 using a two-sided z-test at a significance level of 0.05.

Table 1: Demographic data and vital signs among groups

Parameters		Mortality Group (n = 47)	Survival Group (n = 33)	P-value
Age (y)		68.5 ± 9.4	61.45 ± 14.7	**0.016** ^{t*}
Gender	**M**	27 (57.4)	18 (54.5)	0.797 ^{x2}
	F	20 (42.6)	15 (45.5)	
Comorbidities	**DM**	23 (48.9)	19 (57.6)	0.446 ^{x2}
	HTN	33 (70.2)	24 (72.7)	0.807 ^{x2}
	IHD	13 (27.7)	11 (33.3)	0.586 ^{x2}
	CKD/ESRD	7 (14.9)	4 (12.1)	0.723 ^{x2}
	CLD	3 (6.4)	1 (3.0)	0.498 ^{x2}
MAP (mmHg)		87.6 ± 22.1	90.91 ± 26.0	0.542 ^{t}
HR (B/min)		95.98 ± 19.1	101.15 ± 27.8	0.326 ^{t}
RR		21.74 ± 6.2	19.39 ± 6.7	0.111 ^{t}
Temp (°C)		37.39 ± 0.5	37.37 ± 0.6	0.848 ^{t}

*Data expressed as mean ± SD or n (%); ² = Chi-square test; t = Student t-test; *significant.*

Table 2: Comparison of laboratory markers, GCS and SOFA scores between the groups.

Variable	Mortality Group (n = 47)		Survival Group (n = 33)		P-value z
	range	Median (IQR)	range	Median (IQR)	
CRP	0.75-420	22.5 (8.308-102.25)	1.05-576	21.5 (8.485-145.167)	0.685
Albumin	1.4-4	2.8 (2.525-3.175)	1.6-4.6	3 (2.6-3.5)	0.137
Lactate	0.56-20	2.22 (1.41-4.575	0.5-8	1.6 (1.322-3.085)	0.106
TLC	4.21-52.66	17.3 (12.125-24.342)	2.17-51.9	17.7 (10.657-24.5)	0.977
Creatinine	0.2-10.6	1.9 (1.122-4.55)	0.4-10.5	1.4 (0.775-3.025)	0.145
Procalcitonin	0.08-66	3.2 (1.223-5.7)	0.08-110	1.7 (0.375-4.432)	0.057
CRP/Alb (CAR)	0.227-161.54	8.21 (2.96-37.463)	0.269-192	7.188 (2.568-43.184)	0.807
Lactate/Alb (LAR)	0.181-8.93	0.869 (0.494-1.75)	0.125-3.04	0.57 (0.368-0.999)	**0.044***
GCS	7-15	11 (9.25-13)	10-15	15 (13.75-15)	**< 0.001***
SOFA score	2-12	5 (4-7)	2-10	3 (2-5)	**< 0.001***

*Data are expressed as range, median (IQR); z = Mann-Whitney test; *significant*

2.2. Statistical analysis

SPSS version 27.0 was used to analyze the data. Quantitative data were expressed using the mean ± SD or the median (interquartile range) (IQR). Frequency and percentage were used to present the qualitative data. The chi-square (χ^2) test, the independent-samples t-test, the Mann-Whitney U test, the Pearson's correlation coefficient (r), and the receiver operating characteristic (ROC) curve analysis were utilized where suitable. The area under the ROC curve (AUC-ROC) measure was used to evaluate a parameter's ability to distinguish between the two groups. Statistics were considered significant when the P-value was less than 0.05 with a 95% confidence interval and 5% margin of error.

3. RESULTS

This prospective study was carried on eighty patients, the patients were followed up and those who survived their icu stay were included in the survival group (33 patients) and those who did not were included in the mortality group (47 patients).

The groups were compared based on demographic data, including age, sex, and comorbidities. The mortality group showed higher age than the survival group with P-value 0.016. Also, groups were comparable in hemodynamic profiles, including mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and temperature (Temp) as demonstrated in Table 1.

Laboratory markers including CRP, albumin, lactate, total leukocytic count (TLC), procalcitonin, creatinine, LAR and CAR were compared between the groups, revealing no statistically significant differences, except for LAR, which showed a significantly higher value in the mortality group vs the survival group (P = 0.044). Furthermore, the mortality group exhibited a significantly higher SOFA score (P < 0.001) and a significantly lower Glasgow coma scale (GCS) compared to the survival group (P < 0.001), as presented in Table 2.

The mortality group showed significant higher requirements of cardiovascular support, mechanical ventilation and renal replacement therapy with P < 0.001, < 0.001, and 0.039 respectively. Moreover, the mortality group exhibited longer duration of cardiovascular support in comparison with the survival group (P < 0.001). Additionally, there was statistically significant increase in ICU stay in the mortality group than the survival group (P < 0.001), as shown in Table 3.

ROC analysis was conducted to assess markers' ability to predict mortality. The AUC for LAR was higher at 0.633 compared to 0.484 for CAR as shown in Table 4. Also as demonstrated in Figure 1.

Table 3: Comparison between the groups concerning cardiovascular support requirements & duration, mechanical ventilation support requirements & duration and ICU stay.

Parameter	Mortality Group (n = 47)		Survival Group (n = 33)		P-value
Cardiovascular support	45 (95.7)		10 (30.3)		**< 0.001** ^{x2*}
Mechanical ventilation support	47 (100)		3 (9.1)		**< 0.001**^{x2*}
Renal replacement therapy	17 (36.2)		5 (15.15)		**0.039** ^{x2*}
Period	**Range**	**Median (IQR)**	**Range**	**Median (IQR)**	**P-value**
Cardiovascular support (days)	1-26	6 (3-9)	1-4	2.5 (1-3)	**< 0.001** ^{z*}
Mechanical ventilation support (days)	1-40	6 (2-12.75)	5-10	10 (6.25-10)	0.712 ^{z}
ICU stay (days)	1-45	12 (7.25-19.75)	2-30	5 (3.75-7.25)	**< 0.001** ^{z} *

*Data are expressed as median range and IQR or proportion; x2 = chi square test; z = Mann-Whitney test; *significant*

Table 4: ROC analysis

	AUC	Cut off	Sensitivity %	Specificity %
CRP	0.473	≥ 128	17	72.7
Alb	0.598	≤ 2.9	66	57.6
Lactate	0.607	> 1.8	61.7	60.6
TLC	0.502	> 10.7	83	27.3
procal	0.626	> 2.3	70.2	66.7
CRP/Albumen (CAR)	0.484	≥ 1.54	89.4	21.2
Lactate/Albumen (LAR)	0.633	> 0.68	63.8	57.6

The CRP/Albumen ratio (CAR) showed a significantly strong positive correlation with CRP (r = 0.989, P < 0.001) and a positive correlation with procalcitonin (r = 0.377, P = 0.001). Meanwhile, the LAR correlated strongly and positively with lactate (r = 0.964, P < 0.001), as detailed in Table 5.

4. DISCUSSION

In the current study, the utility of LAR and CAR as predictors of mortality in patients with sepsis requiring ICU admission was investigated. Our findings revealed that, in sepsis patients, LAR was a more reliable predictive factor for mortality than CAR. LAR showed a significant difference between the survivor and non-survivor groups (P = 0.044 vs 0.807, respectively). When compared to CAR (0.484), LAR's AUC for predicting mortality in ROC analysis was higher at 0.633. The optimal cutoff value for LAR (> 0.68 ng/ml) provided a sensitivity of 63.8% and specificity of 57.6%, while for CAR (> 85 ng/ml), sensitivity was 4.3% and specificity was 78.8%. This superiority of LAR may be attributed to lactate's role as a more indicative marker of cellular

Table 5: correlation between parameters

		CRP	Alb	Lactate	TLC	procal	SOFA	CRP/Alb	Lac/Alb
CRP/Alb	**R**	0.989	-0.246	-0.065	0.051	0.377	-0.167		-0.058
	P-value	<0.001	0.028	0.565	0.655	0.001	0.138		0.607
Lactate/Alb	**R**	-0.101	-0.236	0.964	-0.079	-0.021	0.186	-0.058	
	P-value	0.372	0.035	<0.001	0.485	0.851	0.099	0.607	

r = Spearman rank correlation coefficient

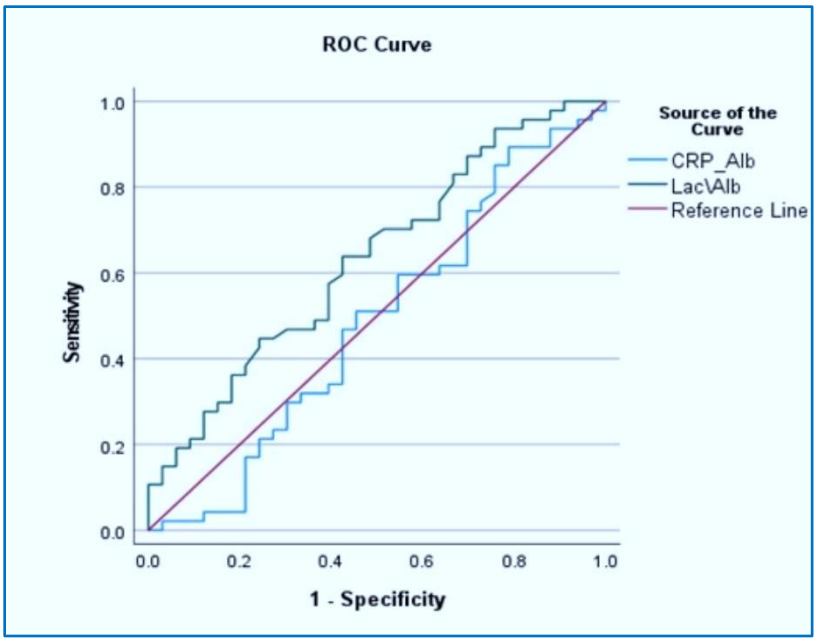

Figure 1: Area under curve (AUC) for LAR was higher 0.633 compared to 0.484 for CAR

hypoperfusion compared to CRP, which primarily reflects inflammatory response. Previous research, including meta-analyses and specific studies, consistently identified LAR as a reliable independent predictor of mortality in sepsis patients in the ICU setting.

Kyung Hun Yoo et al. (2024) conducted a study involving 3,499 sepsis patients with a mortality rate of 77.4%, reporting an AUC of 0.715 for LAR.[6] Kabra et al. studied 160 sepsis cases with a mortality rate of 41.2%, finding an AUC of 0.976 for LAR.[8] A meta-analysis by Yoon et al., which included eight studies involving 4,723 patients, reported an AUC of 0.74 for LAR.[14] Additionally, Esra & Turan investigated 1,136 sepsis patients with a mortality rate of 42.7%. Their ROC analysis identified optimal cut-off values and AUCs as follows: 0.816 and >2.2 mmol/L for lactate, 0.812 and ≤ 26 g/L for albumin, and 0.869 for LAR (> 0.71 ng/ml).[15] These studies collectively emphasize the predictive value of LAR in assessing mortality risk among sepsis patients.

Previous studies have directly compared LAR and CAR as predictors of mortality specifically in patients with septic shock. However, a study conducted by Sai et al. compared the prognostic abilities of LAR and CAR in 100 patients admitted to critical care units with various diagnoses.[16] Sai et al. claimed that CAR was better than LAR in predicting mortality, especially in patients requiring inotropes and mechanical ventilation, which is contrary to the results of the current study. It was shown that 0.84 was the ideal cutoff for LAR, yielding 76.9% sensitivity and 83.8% specificity. In a similar vein, CAR demonstrated a 98.6% specificity and 84.6% sensitivity with an optimal cutoff of 88.2 ng/ml. Notably, it was discovered that patients had a greater mortality risk when their LAR and CAR values were raised.

In a study carried by Zhou et al. 2023, on 6414 sepsis patients , ROC curve analysis revealed that the AUC of CAR was 0.881.[17] Also, in a study carried by Krishnamurthy & Kishor,on 100 patients with sepsis, the mortality was 27%, The serum CAR , positively correlated with the outcome of sepsis and septic shock.[11] Moreover , in a study carried by Kim et al., on 670 sepsis patients, the mortality rate was 28.35% . Moreover, AUC for 180 days mortality for CAR and CRP alone were 0.6211 and 0.5620 respectively.[18]

Based on the aforementioned studies, it is evident that LAR serves as a reliable independent predictor of mortality in sepsis patients admitted to the ICU. Previous studies have demonstrated the prognostic value of LAR and CAR for mortality in a variety of ICU patients, including those with and without sepsis.

In the study carried by Zarazúa et al. on 490 COVID-19 patients, the diagnostic accuracy of both lactate and LAR for mechanical ventilation (MV) was high (AUC 0.964 and 0.946, respectively) and mortality (AUC 0.926 and 0.887, respectively).[19] Similarly, Genç & Toçoğlu studied 535 COVID-19 patients and found LAR to be a reliable marker for mortality in ICU-admitted COVID-19 patients, with an AUC of 0.719 for identifying those at risk of MV.[20] These studies underscore the utility of LAR and CAR in predicting outcomes in critically ill patients.

Wang et al. conducted a study on 1,134 acute myocardial infarction patients, finding an AUC of 0.725 for LAR in predicting 28-day mortality.[21] Dudoignon et al. studied 471 severely ill burn patients and demonstrated that LAR at admission had an AUC of 0.81 for discriminating 28-day mortality, comparable to the SOFA score's AUC of 0.80.[22] Amin Gharipour et al. investigated 6,414 ICU patients with hepatic and renal dysfunction, showing that LAR had an ROC-AUC value of 0.69 for predicting ICU mortality, higher than lactate alone with an ROC-AUC of 0.67. LAR was recognized as a reliable marker for ICU mortality particularly in patients with altered lactate elimination.[23]

In the current study, factors such as MV requirement, duration of ICU stay, SOFA score, need for vasopressor support, Glasgow Coma Scale (GCS), age, and requirement for renal replacement therapy (RRT) were significantly higher in the mortality group. Previous research has explored the associations of these factors with mortality outcomes.[24]

Kaushik et al. 2023, in a study involving 309 sepsis patients, observed that older age was associated with prolonged ICU stays exceeding one week (P = 0.041). However, they did not find significant associations between age, gender, number of co-morbidities, presence of septic shock, multi-organ failure and survival outcomes.[25]

Thakur et al. studied 119 patients with a mortality rate of 60% and found high rates of inotropic use (63.96%) and MV requirement (69.61%). Their analysis revealed a significant association (P < 0.001) between SOFA score and mortality, particularly in patients with sepsis, requiring inotropes, and needing MV, which collectively contributed to high mortality rates.[26]

In contrast, Klein et al. conducted a study involving 691 patients, suggesting that the duration of in-hospital ventilation in sepsis patients who survived hospitalization does not impact mortality. Their study focused on patients who were ventilated for up to 60 days in the general ICU. They found that age, diabetes mellitus, and the need for MV were associated with increased mortality risk (P < 0.001, P = 0.01, P = 0.544, respectively).[27]

Several studies have investigated the SOFA score as a prognostic marker for mortality in sepsis and septic patients. Kari et al. studied 292 patients and reported significant associations between ICU mortality and Glasgow Coma Scale (GCS), SOFA scores, and the need for renal replacement therapy (RRT) (P = 0.019, P < 0.001, P < 0.001, respectively).[28,29,30] It has been concluded that RRT did not reduce 90-day mortality in septic cases with AKI. However, timely initiation of RRT may aid in restoring systemic organ function.[31,32]

5. CONCLUSION

Lactate/albumin ratio demonstrated better performance than C-reactive protein/albumin ratio in predicting ICU mortality for patients with sepsis and septic shock.

6. Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

7. Ethics considerations

This study was approved by the research ethics committee at the faculty of medicine, Ain Shams University (FMASU MD287a/2022/2023) and registered with PACTR202312493987501. Written informed consent was obtained from all patients.

8. Competing interests

The authors declare that there were no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

9. Authors' contribution

All authors have contributed intellectually to the manuscript and the manuscript has been read and approved by all the authors. All authors read and approved the final manuscript.

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